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Transformations of 5-Chloro-2-hydrazino-4-*p*-tolylsulfonyl-1,3-thiazole

K. V. Turov, T. K. Vinogradova, and B. S. Drach

Institute of Bioorganic and Petroleum Chemistry, National Academy of Sciences of Ukraine, ul. Murmanskaya 1, Kiev, 02660 Ukraine
e-mail: drach@bpci.kiev.ua

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Abstract—Accessible 2,2-dichloro-1-*p*-tolylsulfonylethenyl isothiocyanate reacted with hydrazine hydrate to give 5-chloro-2-hydrazino-4-*p*-tolylsulfonyl-1,3-thiazole whose reactions with thiols and amines followed a complicated pattern. Treatment of 5-chloro-2-hydrazino-4-*p*-tolylsulfonyl-1,3-thiazole with acetylacetone led to the formation of previously unknown 5-chloro-2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-*p*-tolylsulfonyl-1,3-thiazole which reacted with O-, S-, and N-centered nucleophiles at the C^5 atom with high regioselectivity.

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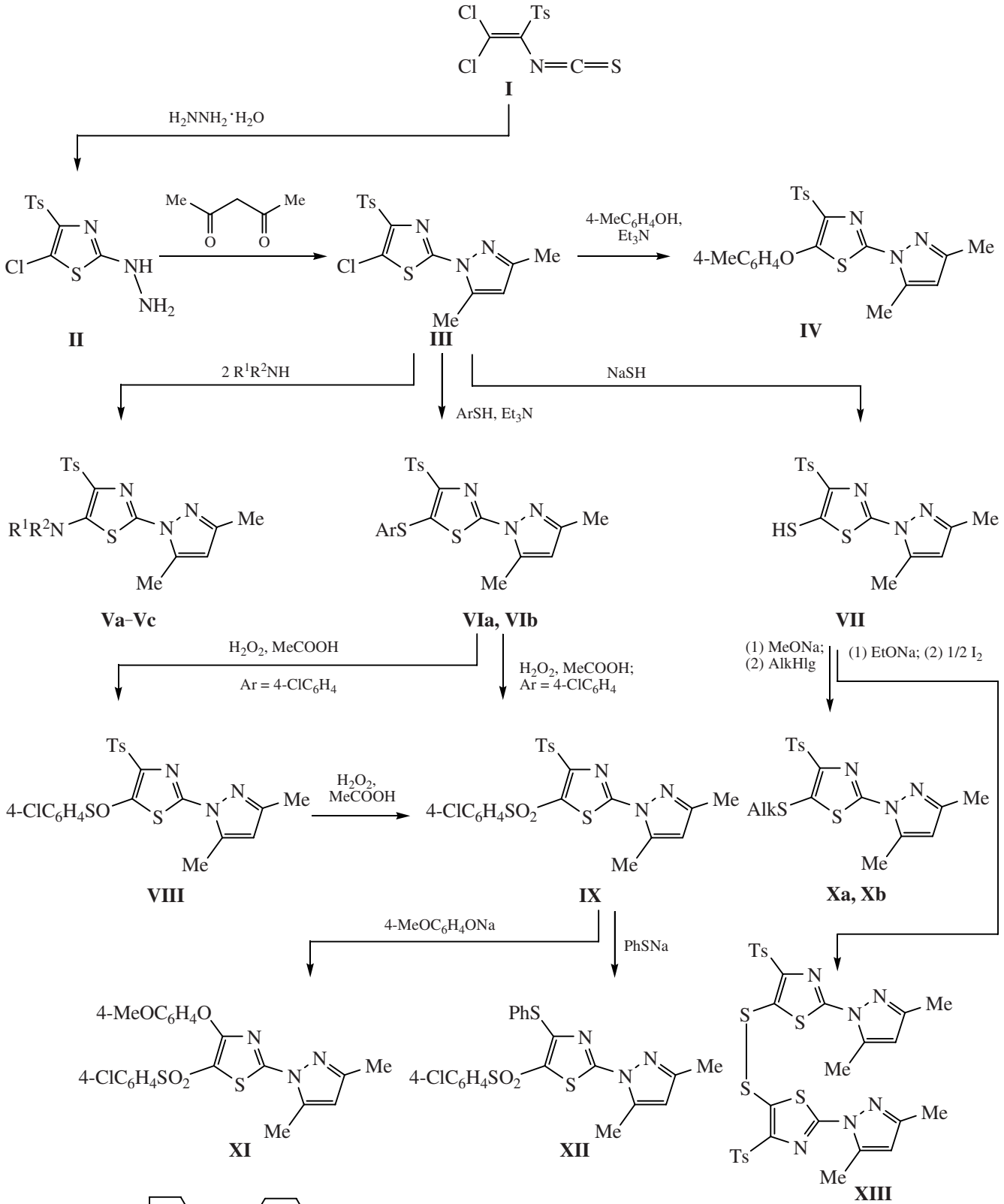
We previously found that 2,2-dichloro-1-*p*-tolylsulfonylethenyl isothiocyanate (**I**) readily reacted with primary and secondary amines to form the corresponding cyclocondensation products, 2-amino-5-chloro-4-*p*-tolylsulfonyl-1,3-thiazole derivatives [1]. Compound **I** reacted with hydrazine hydrate in a similar way (Scheme 1), and this reaction was used as a preparative method for the synthesis of 5-chloro-2-hydrazino-4-*p*-tolylsulfonyl-1,3-thiazole (**II**) [1]. The latter is sufficiently electrophilic to react with aromatic thiols in the presence of triethylamine; however, these reactions were not selective, and mixtures of unidentified products were formed. On the other hand, treatment of substituted 2-hydrazino-1,3-thiazole **II** with acetylacetone readily produces electrophilic compound **III** which is capable of undergoing regioselective condensations with O-, N-, and S-centered nucleophiles (transformations **III** → **IV**, **III** → **V**, **III** → **VI**, and **III** → **VII** in Scheme 1).

These nucleophilic substitution reactions always involved the C^5 atom in the thiazole ring, whereas the tosyl group in the 4-position remained intact; the contribution of other processes was insignificant. Further modification of compounds **VI** and **VII** afforded new functionally substituted 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,3-thiazoles **VIII**–**XII** (Table 1) that are difficult to obtain by other methods.

It should be specially emphasized that the transformation **VI** → **IX** enhances electrophilicity of the thiazole fragment having a tosyl group on C^4 and a *p*-chlorophenylsulfonyl group on C^5. Interestingly, the C^4 atom in molecule **IX** turned out to be the most reactive toward oxygen- and sulfur-centered nucleophiles. We succeeded in demonstrating that the main transformations of **IX** are those involving elimination of the *p*-tolylsulfonyl group, **IX** → **XI** and **IX** → **XII**. The reactivity of **IX** considerably differed from the reactivity of 5-*p*-chlorophenylsulfonyl-2-phenylsulfonyl-4-*p*-tolylsulfonyl-1,3-thiazole which reacted with sulfur nucleophiles at C^2 and C^5 [2].

To conclude, we can state that the structure of compounds **II**–**XII** directly follows from the scheme of their synthesis; in addition, the structure of **II**–**XII** was confirmed by ^{1}H NMR spectroscopy (Table 2). For instance, the formation of 3,5-dimethyl-1*H*-pyrazol-1-yl fragment in the transformation **II** → **III** is readily revealed by the appearance of two singlets from methyl protons in the region δ 2.2–2.6 ppm. Comparison of the ^{1}H NMR spectra of compounds **IX** and **XII** shows that the latter lacks singlet at δ 2.40 ppm as a result of elimination of the tosyl group in the reaction of **IX** with sodium benzenethiolate. Finally, introduction of various R^1R^2N and AlkS groups into the 5-position of the thiazole ring in the synthesis of compounds **Va**–**Vc**, **Xa**, and **Xb** gives rise to the corresponding signals in the ^{1}H NMR spectra (Table 2).

Scheme 1.



V, R^1R^2N = N (**a**), O N (**b**), $PhCH_2NH$ (**c**); **VI**, Ar = 4-MeC_6H_4 (**a**), 4-ClC_6H_4 (**b**); **V**, Alk = Me (**a**), *i*-Pr (**b**).

Table 1. Yields, melting points, and elemental analyses of compounds **II**–**XIII**

Comp. no.	Yield, %	mp, °C (solvent)	Found, %			Formula	Calculated, %		
			Cl	S	N		Cl	S	N
II	70	205–207 (EtOH)	11.70	21.03	13.05	$C_{10}H_{10}ClN_3O_2S_2$	11.67	21.11	13.83
III	85	135–136 (EtOH)	9.58	17.47	11.32	$C_{15}H_{14}ClN_3O_2S_2$	9.64	17.43	11.42
IV	71	283–284 (EtOH)	–	14.55	9.40	$C_{22}H_{21}N_3O_3S_2$	–	14.59	9.56
Va	68	183–184 (EtOH)	–	16.02	13.80	$C_{19}H_{22}N_4O_2S_2$	–	15.93	13.92
Vb	70	152–154 (EtOH)	–	15.80	13.75	$C_{19}H_{22}N_4O_3S_2$	–	15.32	13.39
Vc	75	181–182 (EtOH)	–	14.58	12.80	$C_{22}H_{22}N_4O_2S_2$	–	14.62	12.77
VIa	76	185–187 (DMF–EtOH, 1:10)	–	21.10	9.18	$C_{22}H_{21}N_3O_2S_3$	–	21.11	9.22
VIb	84	168–170 (DMF–EtOH, 1:10)	7.50	20.27	8.90	$C_{21}H_{18}ClN_3O_2S_3$	7.45	20.21	8.83
VII	87	202–205	–	26.32	11.21	$C_{15}H_{15}N_3O_2S_3$	–	26.32	11.50
VIII[a]	60	158–160 (EtOH)	7.23	19.64	8.67	$C_{21}H_{18}ClN_3O_3S_3$	7.21	19.55	8.54
IX[b]	56	140–142 (EtOH)	7.04	18.97	8.41	$C_{21}H_{18}ClN_3O_4S_3$	6.98	18.93	8.27
Xa	70	185–187 (EtOH)	–	25.43	11.21	$C_{16}H_{17}N_3O_2S_3$	–	25.35	11.07
Xb	75	142–144 (EtOH)	–	23.54	10.18	$C_{18}H_{21}N_3O_2S_3$	–	23.60	10.31
XI	57	210–212 (EtOH)	6.98	13.75	8.52	$C_{21}H_{18}ClN_3O_4S_2$	7.45	13.47	8.83
XII	65	138–140 (EtOH)	7.20	20.99	9.25	$C_{20}H_{16}ClN_3O_2S_3$	7.67	20.82	9.09
XIII	62	185–187 (DMF)	–	27.64	10.95	$C_{28}H_{24}N_6O_4S_6$	–	27.45	11.99

[a] Found, %: C 51.63; H 4.05. Calculated, %: C 51.26; H 3.69. [b] Found, %: C 49.49; H 3.62. Calculated, %: C 49.65; H 3.57.

Table 2. ^{1}H NMR spectra of compounds **II**–**XIII** (DMSO-d_6)

Comp. no.	Chemical shifts δ, ppm
II	2.44 s (3H, CH_3), 5.03 br.s (2H, NH_2), 7.38–7.40 m (2H$_{arom}$), 7.77–7.79 m (2H$_{arom}$), 9.14 br.s (1H, NH)
III	2.20 s (3H, CH_3), 2.44 s (3H, CH_3), 2.53 s (3H, CH_3), 5.96 s (1H, CH), 7.34–7.36 m (2H$_{arom}$), 7.95–7.97 m (2H$_{arom}$)
IV	2.12 s (3H, CH_3), 2.37 s (3H, CH_3), 2.45 s (3H, CH_3), 2.55 s (3H, CH_3), 6.07 s (1H, CH), 7.09–7.11 m (2H$_{arom}$), 7.23–7.25 m (2H$_{arom}$), 7.40–7.42 m (2H$_{arom}$), 7.83–7.85 m (2H$_{arom}$)
Va	2.04 m (4H, $2CH_2$), 2.13 s (3H, CH_3), 2.20 s (3H, CH_3), 2.41 s (3H, CH_3), 3.53 m (4H, $2CH_2$), 5.93 s (1H, CH), 7.33–7.35 m (2H$_{arom}$), 7.75–7.77 m (2H$_{arom}$)
Vb	2.15 s (3H, CH_3), 2.38 s (3H, CH_3), 2.43 s (3H, CH_3), 3.12 m (4H, $2CH_2$), 3.78 m (4H, $2CH_2$), 6.00 s (1H, CH), 7.37–7.39 m (2H$_{arom}$), 7.81–7.83 m (2H$_{arom}$)
Vc	2.10 s (3H, CH_3), 2.41 s (3H, CH_3), 2.46 s (3H, CH_3), 4.46 m (2H, CH_2), 5.94 s (1H, CH), 7.33–7.36 m (6H$_{arom}$), 7.97–7.81 m (2H$_{arom}$)
VIa	2.09 s (3H, CH_3), 2.40 s (3H, CH_3), 2.44 s (3H, CH_3), 2.48 s (3H, CH_3), 6.01 s (1H, CH), 7.28–7.30 m (2H$_{arom}$), 7.41–7.43 m (2H$_{arom}$), 7.51–7.53 m (2H$_{arom}$), 7.87–7.89 m (2H$_{arom}$)
VIb	2.11 s (3H, CH_3), 2.44 s (3H, CH_3), 2.49 s (3H, CH_3), 6.04 s (1H, CH), 7.41–7.43 m (2H$_{arom}$), 7.47–7.49 m (2H$_{arom}$), 7.59–7.61 m (2H$_{arom}$), 7.87–7.89 m (2H$_{arom}$)
VIII	2.16 s (3H, CH_3), 2.44 s (3H, CH_3), 2.47 s (3H, CH_3), 6.12 s (1H, CH), 7.43–7.45 m (2H$_{arom}$), 7.65–7.67 m (2H$_{arom}$), 7.80–7.82 m (2H$_{arom}$), 7.93–7.95 m (2H$_{arom}$)
IX	2.20 s (3H, CH_3), 2.40 s (3H, CH_3), 2.44 s (3H, CH_3), 6.15 s (1H, CH), 7.39–7.42 m (2H$_{arom}$), 7.72–7.74 m (4H$_{arom}$), 8.12–8.14 m (2H$_{arom}$)
Xa	2.22 s (3H, CH_3), 2.42 s (3H, CH_3), 2.54 s (3H, CH_3), 2.61 (3H, CH_3), 5.95 s (1H, CH), 7.31–7.33 m (2H$_{arom}$), 7.95–7.97 m (2H$_{arom}$)
Xb	1.04–1.07 m (3H, CH_3), 1.74–1.76 m (2H, CH_2), 2.16 s (3H, CH_3), 2.43 s (3H, CH_3), 2.50 s (3H, CH_3), 3.01–3.05 m (2H, CH_2), 6.07 s (1H, CH), 7.39–7.41 m (2H$_{arom}$), 7.83–7.85 m (2H$_{arom}$)
XI	2.21 s (3H, CH_3), 2.27 s (3H, CH_3), 3.78 s (3H, OCH_3), 6.10 s (1H, CH), 6.87–6.89 m (2H$_{arom}$), 7.01–7.03 m (2H$_{arom}$), 7.66–7.68 m (2H$_{arom}$), 8.01–8.03 m (2H$_{arom}$)
XII	2.10 s (3H, CH_3), 2.45 s (3H, CH_3), 6.02 s (1H, CH), 7.37–7.50 m (5H$_{arom}$), 7.60–7.62 m (2H$_{arom}$), 7.87–8.89 m (2H$_{arom}$)
XIII	2.20 s (6H, $2CH_3$), 2.44 s (6H, $2CH_3$), 2.53 s (6H, $2CH_3$), 5.87 s (2H, 2CH), 7.34–7.36 m (4H$_{arom}$), 7.95–7.97 m (4H$_{arom}$)

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury 400 spectrometer using DMSO-d_6 as solvent and tetramethylsilane as internal reference.

5-Chloro-2-hydrazino-4-(*p*-tolylsulfonyl)-1,3-thiazole (II). A solution of 0.5 mol of hydrazine hydrate in 10 ml of THF was added dropwise over a period of 5 min to a solution of 0.05 mol of compound **I** in 10 ml of THF, cooled to 5°C. The mixture was stirred for 5 h at 20°C, the solvent was removed under reduced pressure, and the residue was recrystallized from ethanol.

5-Chloro-2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-(*p*-tolylsulfonyl)-1,3-thiazole (III). Acetylacetone, 0.09 mol, and glacial acetic acid, 0.5 ml, were added to a suspension of 0.03 mol of compound **II** in 10 ml of ethanol. The mixture was heated for 10 h under reflux and cooled to 20°C, and the precipitate was filtered off and recrystallized from ethanol.

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-5-(*p*-tolyloxy)-4-(*p*-tolylsulfonyl)-1,3-thiazole (IV). Compound **III**, 0.01 mol, was dissolved in 10 ml of THF, 0.02 mol of *p*-methylphenol and 0.02 mol of triethylamine were added, and the mixture was heated for 10 h under reflux. The solvent was removed under reduced pressure, and the residue was recrystallized from ethanol.

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-5-(pyrrolidin-1-yl, morpholino, benzylamino)-4-(*p*-tolylsulfonyl)-1,3-thiazoles Va–Vc (*general procedure*). Pyrrolidine, morpholine, or benzylamine, 0.1 mol, was added to a suspension of 0.05 mol of compound **III** in 10 ml of butanol, and the mixture was heated for 20 h under reflux. The solvent was removed under reduced pressure, and the residue was washed with water and recrystallized from ethanol.

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-4-(*p*-tolylsulfonyl)-5-(*p*-tolylsulfanyl, 4-chlorophenylsulfanyl)-1,3-thiazoles VIa and VIb (*general procedure*). *p*-Methyl- or *p*-chlorobenzenethiol, 0.1 mol, and triethylamine, 0.1 mol, were added to a suspension of 0.05 mol of compound **III** in 10 ml of ethanol, and the mixture was heated for 15 h under reflux. The precipitate was filtered off, the solvent was removed from the filtrate under reduced pressure, and the residue was recrystallized from ethanol–DMF (10:1).

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-4-(*p*-tolylsulfonyl)-1,3-thiazole-5-thiol (VII). Freshly prepared hydrogen sulfide, 0.0075 mol, was added to a suspension of 0.0015 mol of compound **III** in 10 ml of methanol, and the mixture was left to stand for 20 h at 20–25°C. The precipitate was filtered off, the solvent was removed from the filtrate under reduced pressure, the residue was treated with 5 ml of water and acidified with concentrated hydrochloric acid to pH 2, and the precipitate was filtered off and used in further syntheses without additional purification.

5-(4-Chlorophenylsulfinyl)-2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-(*p*-tolylsulfonyl)-1,3-thiazole (VIII). Compound **VIb**, 0.01 mol, was dispersed in 5 ml of glacial acetic acid, 0.5 ml of 30% aqueous hydrogen peroxide was added, and the mixture was heated for 0.5 h under reflux. The solvent was removed under reduced pressure, and the residue was recrystallized from ethanol.

5-(4-Chlorophenylsulfonyl)-2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-(*p*-tolylsulfonyl)-1,3-thiazole (IX). *a*. Compound **VIb**, 0.0015 mol, was dispersed in 5 ml of glacial acetic acid, 1 ml of 30% aqueous hydrogen peroxide was added, and the mixture was heated for 2 h under reflux and cooled to 20°C. The precipitate was filtered off and purified by recrystallization from acetic acid.

b. Compound **VIII**, 0.001 mol, was dispersed in 7 ml of glacial acetic acid, 1 ml of 30% aqueous hydrogen peroxide was added, the mixture was heated for 2 h under reflux and cooled to 20°C, and the precipitate was filtered off and purified by recrystallization from acetic acid. Samples of **IX** obtained as described in *a* and *b* showed no depression of the melting point at mixing.

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-5-(methylsulfanyl, isopropylsulfanyl)-4-(*p*-tolylsulfonyl)-1,3-thiazoles Xa and Xb (*general procedure*). Compound **VII**, 0.05 mol, was dispersed in 5 ml of methanol, 0.05 mol of sodium methoxide and 0.065 mol of methyl iodide or isopropyl bromide were added, the mixture was heated for 3 h under reflux, and the precipitate was filtered off and purified by recrystallization from ethanol.

5-(4-Chlorophenylsulfonyl)-2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-(4-methoxyphenoxy)-1,3-thiazole (XI). Compound **IX**, 0.05 mol, was dissolved in 10 ml of THF, 0.1 mol of sodium 4-methoxyphenoxide was added, and the mixture was left to stand for 24 h at 20°C. The solvent was removed under reduced pressure, and the residue was recrystallized from ethanol.

5-(4-Chlorophenylsulfonyl)-2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-phenylsulfanyl-1,3-thiazole (XII). Compound **IX**, 0.05 mol, was dispersed in 10 ml of THF, 0.1 mol of sodium benzenethiolate was added, and the mixture was left to stand for 24 h at 20–25°C. The solvent was removed under reduced pressure, and the residue was recrystallized from ethanol.

5,5′-Dithiobis[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-(*p*-tolylsulfonyl)-1,3-thiazole] (XIII). Compound **VII**, 0.01 mol, was dispersed in 10 ml of ethanol, a solution of 0.01 mol of sodium ethoxide in 3 ml of ethanol and 16 ml of a 3% solution of iodine in ethanol were added, and the mixture was left to stand for 48 h at 20°C. The solvent was removed under reduced pressure, and the residue was recrystallized from ethanol–DMF (10:1).

REFERENCES

1. Babii, S.B., Zyabrev, V.S., and Drach, B.S., *Russ. J. Gen. Chem*., 2002, vol. 72, no. 11, p. 1730.

2. Turov, K.V., Vinogradova, T.K., Zyabrєv, V.S., and Drach, B.S., *Tezi dopovidei XXI Ukraïns'koï konferentsiï z organichnoï khimiï* (Abstracts of Papers of the XXIth Ukrainian Conf. on Organic Chemistry), Chernigiv, 2007, p. 336.